Kansas Drug Utilization Review Newsletter

Health Information Designs, LLC **Winter 2014**

Welcome to the winter 2014 edition of the "Kansas Drug Utilization Review Newsletter," published by Health Information Designs, LLC (HID). This newsletter is part of a continuing effort to keep the Medicaid provider community informed of important changes in the Kansas Medical Assistance Program (KMAP).

Non-Steroidal Anti-Inflammatory Agents

NSAID Mechanism of Action

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) are one of the most widely used drug classes. They are used to treat fever, inflammation, and pain associated with many disease states. NSAIDs inhibit the activity of the Cyclooxygenase (COX) enzyme. COX enzyme activity leads to the formation of prostaglandins (PGs). PGs are responsible for many different roles within our bodies, from inflammation, pain, swelling, and fever to protecting the stomach mucosa from damage by hydrochloric acid, maintaining kidney function, and platelet aggregation. By inhibiting the COX enzymes NSAIDs inhibit the formation of PGs. This mechanism of action provides an explanation for the therapeutic actions and shared side effects of NSAIDs. There are two isoforms of the COX enzyme:

- COX-1 is a constitutive enzyme and is found on most cells and supports beneficial homeostatic functions such as protecting the stomach mucosa.
- COX-2 is an inducible enzyme that is normally undetectable but becomes abundant at sites of inflammation, its products cause many of the symptoms of inflammatory diseases such as rheumatoid and osteoarthritis

Non-Selective and Selective NSAIDs

Non-selective NSAIDs competitively and reversibly inhibit both COX-1 and COX-2 enzymes. Because of the competitive and reversible inhibition of COX-1, the non-selective NSAIDs do not cause significant inhibition of platelet aggregation as seen with aspirin use. Since the non-selective agents inhibit both forms of COX, they do possess therapeutic and side effect profiles associated with each mechanism of inhibition.

Aspirin is a potent cardiovascular protective agent and is used today to prevent occlusive cardiovascular disease. Aspirin permanently inhibits the COX-1 enzyme by non-competitive and irreversible binding, helping to cause the unique effect of inhibiting platelet aggregation.

COX-2 selective NSAIDs were developed to inhibit COX-2 (reducing pain and inflammation) without inhibiting COX-1, which would minimize the gastrointestinal (GI) side effects seen with COX-1 inhibition. The irreversible covalent binding of COX-2, however, impairs the synthesis of endothelium-derived antithrombotic and vasodilatory prostacyclin. This impairment can cause thrombogenesis and vasoconstriction, leading to adverse cardiovascular (CV) effects.

NSAID Risks

NSAIDs are commonly prescribed, but their use can be limited by adverse drug events associated with this class of medications. As a class, NSAIDs are associated with a range of side effects that can include renal toxicity, hepatotoxicity, exacerbation of hypertension, fluid retention, GI complications, and CV events. High doses, prolonged use, and therapeutic duplication of NSAIDs can lead to an increase in adverse events and complications associated with this drug class. For the purpose of this article, we will focus on GI and CV complications caused by NSAIDs. ***Continued on Page 2.***

In This Issue

Helpful Web Sites

KMAP Web Site
https://www.kmap-state-ks.us/

KDHE-DHCF Web Site
http://www.kdheks.gov/hcf/

KanCare Web Site
http://www.kancare.ks.gov/

Fee-For-Service (FFS) Helpful Numbers

Provider Customer Service
(Provider Use Only)
1-800-933-6593

Beneficiary Customer Service
1-800-766-9012

KMAP PA Help Desk
1-800-285-4978

Please send questions or comments regarding this newsletter to KSDURNewsletter@hidinc.com

Non-Steroidal Anti-Inflammatory Agents (continued)

Continued from page 1.

GI Complications

Because of the inhibition of COX-1, aspirin and the non-selective NSAIDs share a similar side effect profile. In general, it is recommended that patients with GI risk factors (Table 1) be treated with COX-2 selective agents or non-selective NSAIDs plus concurrent gastroprotective therapy. Gastroprotective therapy agents include H-2 antagonists, misoprostol, and Proton Pump Inhibitors (PPIs).

Table 1: Patients at Risk for Developing GI Bleeds

Patients with a previous GI bleed
Patients > 60 years of age
Patients receiving a high dose of NSAIDs
Patients with concurrent use of corticosteroids, aspirin, anticoagulants, platelet inhibitors, and SSRIs
Patients with *Helicobacter pylori* infections
Patients with comorbid diabetes, heart failure, and rheumatoid arthritis

CV Complications

Recently, there has been an increased awareness of CV risk associated with the use of NSAIDs, excluding aspirin, especially in patients with a history of CV disease. NSAIDs currently carry the following black box warning from the FDA, "Cardiovascular Risk: NSAIDs may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at a greater risk."

NSAID use is associated with an increased risk of hypertension, edema, congestive heart failure, and myocardial infarction. The risk appears to be dependent on the duration of exposure. Both COX-2 selective agents and non-selective NSAIDs inhibit COX-2 at traditional doses and have the potential to cause CV toxicity. Therefore, COX selectivity does not define the risk of NSAID-associated CV complications. The American Heart Association and the American College of Rheumatology recommend that all NSAIDs, particularly COX-2 selective agents, be avoided in patients with CV risk factors. In addition they should be used only when sufficient pain relief is not achieved with other therapies and when the benefit outweighs the increased CV risk. Where NSAID therapy is required for patients at risk for CV complications, naproxen is recommended as the NSAID of choice.

CV risk factors include: hypertension, hypercholesterolemia, angina, edema, recent bypass surgery, history of myocardial infarction, or other CV events. Meek et al. published an algorithm to assist in the selection of an NSAID based on a patient's GI & CV risk factors. The algorithm was published in a 2010 issue of *Pharmaceuticals* (Table 2).

Table 2: Selection of Appropriate NSAID

	Low GI Risk	Moderate GI Risk (1–2 risk factors)	High GI Risk (> 2 risk factors)
Low CV Risk*	Non-Selective NSAIDs	Non-Selective NSAID + PPI** or COX-2 + PPI**	COX-2 + PPI**
High CV Risk*	Naproxen + PPI**	Naproxen + PPI**	No NSAID

*Evaluation of CV risk is according to the judgment of the prescriber. Patients with high CV risk should receive prophylactic low-dose aspirin. If additional NSAID therapy is required, naproxen is the preferred NSAID. Naproxen should be taken 2 hours after aspirin.

**PPI can be substituted with misoprostol 400–800 mg or an H-2 antagonist.

Conclusion

NSAIDs are effective at treating mild to moderate pain. Drugs within the class provide unique options for individual patients and their concurrent disease states. Non-selective NSAIDs pose an increased risk of GI side effects, and both non-selective NSAIDs and COX-2 inhibitors have been shown to increase rates of CV events. In general practice, a patient's GI and CV status should be taken into account when choosing the right treatment and the lowest dose and shortest duration should be used.

References

Antman EM, Bennett JS, Daugherty A, et al. Use of nonsteroidal anti-inflammatory drugs: an update for clinicians: a scientific statement from the American Heart Association. Circulation 2007; 115:1634–42.

Chan FK. Primer: managing NSAID-induced ulcer complications-balancing gastrointestinal and cardiovascular risks. *Nat Clin Pract Gastroenterol Hepatol*. 2006; 3:563–73.

Conaghan PG. A turbulent decade for NSAIDs: update on current concepts of classification, epidemiology, comparative efficacy, and toxicity. *Rheumatol Int*. December 2011.

Desai SP, Solomon DH, Abramson SP, et al. Recommendations for use of selective and nonselective nonsteroidal anti-inflammatory drugs: an American College of Rheumatology white paper. *Arthritis Rheum*. 2008, 59:1058-1073.

Lanza FL, Chan FK, Quigley EM. Guidelines for prevention of NSAID-related ulcer complications. *Am J Gastroenterol*. 2009; 104:728–38.

Meek IL, Van de Laar MA, Vonkeman HE. Non-steroidal anti-inflammatory drugs: an overview of cardiovascular risks. *Pharmaceuticals*. 2010; 3:2146–62.

Scheiman JM, Fendrick AM. Summing the risk of NSAID therapy. *Lancet*. 2007; 369:1580–1581.

Warner TD, Mitchell JA. COX-2 selectivity alone does not define the cardiovascular risks associated with nonsteroidal anti-inflammatory drugs. *Lancet*. 2008; 371:270–73.

Preferred Drug List

The Preferred Drug List (PDL) is maintained by KDHE-DHCF. Each MCO and KMAP follow the same PDL. Below is a list of current preferred agents. A complete list of both preferred and non-preferred agents may be found on the KDHE-DHCF Web site. The Preferred Drug List is typically updated on the first of each month; please visit the KDHE-DHCF Web site for the most recent version: http://www.kdheks.gov/hcf/pharmacy/pharmacy_druglist.html.

Allergy, Asthma, & COPD Agents

Anticholinergics for the Maintenance of COPD
Spiriva® (tiotropium)

Combination Products for Allergic Rhinitis
Dymista® (azelastine/fluticasone)

Short-Acting Beta$_2$-Agonists
AccuNeb® (albuterol)
ProAir HFA® (albuterol)
Proventil® (albuterol)
Ventolin® (albuterol)

Long-Acting Beta$_2$-Agonists
Clinical PA may be required
Foradil® (formoterol)
Serevent® (salmeterol)

Inhaled Long-Acting Beta$_2$-Agonists/Corticosteroids
Advair® (fluticasone/salmeterol)
Dulera® (formoterol/mometasone)

Inhaled Corticosteroids
Asmanex® (mometasone)
Flovent® (fluticasone)
Pulmicort Respules® (budesonide)
***≤6 years of age only**
QVAR® (beclomethasone)

Intranasal Corticosteroids
Flonase® (fluticasone)
Nasonex® (mometasone)
Qnasl® (beclomethasone)
Veramyst® (fluticasone)

Intranasal Antihistamines
Astelin® (azelastine)
Patanase® (olopatadine)

Non-Sedating Antihistamines
Claritin® (loratadine)
Zyrtec® (cetirizine)

Ophthalmic Antihistamine/Mast Cell Stabilizer Combinations
Alaway® (ketotifen)
Pataday® (olopatadine)
Patanol® (olopatadine)
Refresh® (ketotifen)
Zaditor® (ketotifen)

Analgesics

Long-Acting Opioids
MS Contin® (morphine sulfate ER)
OxyContin® (oxycodone SR)

Muscle Relaxants (Skeletal)
Flexeril® (cyclobenzaprine)
Parafon Forte DSC® (chlorzoxazone)
Robaxin® (methocarbamol)
Robaxin-750® (methocarbamol)
Robaxisal® (methocarbamol/aspirin)

Muscle Relaxants (Spasticity)
Lioresal® (baclofen)
Zanaflex® (tizanidine)
***tablets only**

Analgesics (continued)

Ophthalmic NSAIDs
Acular® (ketorolac)
Acular LS® (ketorolac)
Acuvail® (ketorolac)
Ilevro® (nepafenac)
Nevanac® (nepafenac)
Ocufen® (flurbiprofen)
Voltaren® Ophthalmic (diclofenac)

Oral NSAIDs
Advil® (ibuprofen)
Aleve® (naproxen)
Anaprox® (naproxen)
Anaprox DS® (naproxen)
Ansaid® (flurbiprofen)
Cataflam® (diclofenac potassium)
Clinoril® (sulindac)
EC-Naprosyn® (naproxen)
Feldene® (piroxicam)
***branded products only**
Indocin® (indomethacin)
Lodine® (etodolac)
Mobic® (meloxicam)
Motrin® (ibuprofen)
Motrin IB® (ibuprofen)
Naprelan® (naproxen)
Naprosyn® (naproxen)
Orudis® (ketoprofen)
Orudis KT® (ketoprofen)
Oruvail® (ketoprofen)
Relafen® (nabumetone)
Tolectin DS® (tolmetin)
Tolectin 600® (tolmetin)
Toradol® (ketorolac)
***limited to a 5 day supply**
Voltaren® (diclofenac)
Voltaren® XR (diclofenac)

Topical NSAIDs
Pennsaid® (diclofenac)
Voltaren® Gel (diclofenac)

Triptans
Amerge® (naratriptan)
Axert® (almotriptan)
Imitrex® (sumatriptan)
***tablets only**
Relpax® (eletriptan)

Antihyperlipidemics

Bile Acid Sequestrants
Colestid® (colestipol)
Prevalite® (cholestyramine)
Questran® (cholestyramine)
Questran® Light (cholestyramine)

Fibric Acid Derivatives
Fenofibrate generics
Lopid® (gemfibrozil)

Statins
Lipitor® (atorvastatin)
Lovastatin generics
Mevacor® (lovastatin)
Pravachol® (pravastatin)
Zocor® (simvastatin)

Anti-Infectives

Antiherpes Virus Agents
Zovirax® (acyclovir)
***oral dosage forms only**

Hepatitis C Protease Inhibitors
Incivek® (telaprevir)
Victrelis® (boceprevir)

Biologics

Adult Rheumatoid Arthritis
*Clinical PA may be required
Enbrel® (etanercept)
Humira® (adalimumab)

Ankylosing Spondylitis
*Clinical PA may be required
Enbrel® (etanercept)
Humira® (adalimumab)

Crohn's Disease
*Clinical PA may be required
Humira® (adalimumab)
Remicade® (infliximab)

Juvenile Idiopathic Arthritis
*Clinical PA may be required
Enbrel® (etanercept)
Humira® (adalimumab)

Plaque Psoriasis
*Clinical PA may be required
Enbrel® (etanercept)
Humira® (adalimumab)

Psoriatic Arthritis
*Clinical PA may be required
Enbrel® (etanercept)
Humira® (adalimumab)

Ulcerative Colitis
*Clinical PA may be required
Humira® (adalimumab)
Remicade® (infliximab)

Cardiovascular Agents

ACE Inhibitors
Accupril® (quinapril)
Capoten® (captopril)
Lotensin® (benazepril)
Monopril® (fosinopril)
Prinivil® (lisinopril)
Vasotec® (enalapril)
Zestril® (lisinopril)

ACE Inhibitors/CCB Combos
Lotrel® (benzapril/amlodipine)

ARBs
Benicar® (olmesartan)
Benicar® HCT (olmesartan/HCTZ)
Cozaar® (losartan)
Diovan® (valsartan)
Diovan® HCT (valsartan/HCTZ)
Hyzaar® (losartan/HCTZ)
Micardis® (telmisartan)
Micardis® HCT (telmisartan/HCTZ)

ARB/CCB Combos
Azor® (amlodipine/olmesartan)
Exforge® (amlodipine/valsartan)

Cardiovascular Agents (continued)

Beta-Blockers
Betapace® (sotalol)
Betapace AF® (sotalol AF)
Blocadren® (timolol)
Coreg® (carvedilol)
Corgard® (nadolol)
Inderal® (propranolol)
InnoPran® XL (propranolol XL)
Kerlone® (betaxolol)
Lopressor® (metoprolol tartrate)
Propranolol® Intensol (propranolol)
Sectral® (acebutolol)
Tenormin® (atenolol)
Toprol® XL (metoprolol succinate)
Visken® (pindolol)

CCBs (Dihydropyridines)
Adalat CC® (nifedipine ER)
Cardene® (nicardipine IR)
DynaCirc® (isradipine)
DynaCirc® CR (isradipine)
Norvasc® (amlodipine)
Procardia® XL (nifedipine ER)

CCBs (Non-Dihydropyridines)
Calan® (verapamil IR)
Calan® SR (verapamil SR)
Cardizem® (diltiazem IR)
Covera HS® (verapamil)
***branded products only**
Diltia XT® (diltiazem)
***brand & AB-rated generics**
Isoptin® SR (verapamil SR)
Tiazac® (diltiazem)
***brand & AB-rated generics**
Verelan® (verapamil SR)

Central Nervous System Agents

Adjunct Antiepileptics
Gabitril® (tiagabine)
Keppra® (levetiracetam)
Keppra® XR (levetiracetam XR)
Lyrica® (pregabalin)
Neurontin® (gabapentin)
Zonegran® (zonisamide)

Non-Benzo Sedative Hypnotics
Ambien® (zolpidem)
Zolpidem generics

Non-Scheduled Sleep Agents
Rozerem® (remelteon)

Diabetic Agents

Alphaglucosidase Inhibitors
Glyset® (miglitol)

Biguanides
Glucophage® (metformin)
Metformin ER generics

Dipeptidyl Peptidase-4 Inhibitors
Januvia® (sitagliptin)
Onglyza® (saxagliptin)
Tradjenta® (linagliptin)

Incretin Mimetics
Clinical PA may be required
Byetta® (exenatide)
Victoza® (liraglutide)

The list of preferred drugs is continued on page 4. This list was updated on **2/1/2014**. Please visit the KDHE-DHCF Web site for the most current version. Please note that when a generic product is available for a preferred or non-preferred agent, the pharmacy will receive a lower reimbursement rate for the branded product unless a DAW PA is approved.

Preferred Drug List

Continued from page 3.

Diabetic Agents (continued)

Insulin Delivery Systems
All multi-dose vials
Novolog® PenFill & FlexPen
Novolog® Mix PenFill & FlexPen

Long-Acting Insulin (Vials Only)
Lantus® (insulin glargine)

Meglitinides
Prandin® (repaglinide)
Starlix® (nateglinide)

2nd Generation Sulfonylureas
Amaryl® (glimepiride)
DiaBeta® (glyburide)
Glucotrol® (glipizide)
Glucotrol® XL (glipizide XL)
Glucovance® (glyburide/metformin)
Glynase PresTab® (micronized glyburide)
Micronase® (glyburide)

SGLT2 Inhibitors
Invokana® (canagliflozin)

Thiazolidinediones
Actos® (pioglitazone)
ACTOplus Met® (pioglitazone/metformin)
ACTOplus Met® XR (pioglitazone/metformin)
Avandia® (rosiglitazone)

Gastrointestinal Agents

H_2 Antagonists
Pepcid® (famotidine)
Zantac® (ranitidine)

Pancreatic Enzyme Replacements
Creon® (pancrelipase)
Ultresa® (pancrelipase)
Viokace® (pancrelipase)
Zenpep® (pancrelipase)

Proton Pump Inhibitors
Prilosec® (omeprazole)
Protonix® (pantoprazole)

Serotonin $5HT_3$ Antagonists
Zofran® (ondansetron)
Zofran® ODT (ondansetron)

Gout Agents

Xanthine Oxidase Inhibitors
Zyloprim® (allopurinol)

Injectables

Erythropoiesis-Stimulating Agents
Epogen® (epoetin alfa)
Procrit® (epoetin alfa)

Injectables (continued)

Growth Hormones
**Clinical PA may be required*
Genotropin® (somatropin)
Genotropin® MiniQuick (somatropin)
Omnitrope® (somatropin)
Saizen® (somatropin)
Tev-Tropin® (somatropin)

Ophthalmic Agents

Ophthalmic Prostaglandin Analogs
Travatan Z® (travoprost)
Xalatan® (latanoprost)
Zioptan® (tafluprost)

Osteoporosis Agents

Bisphosphonates
Fosamax® (alendronate)
Fosamax Plus D® (alendronate/cholecalciferol)

Urologic Agents

Anticholinergic Agents
Detrol® (tolterdine)
Detrol® LA (tolterodine ER)
Ditropan® (oxybutynin)
Toviaz® (fesoterodine)
Vesicare® (solifenacin)

Beta-3 Adrenergic Agonists
Myrbetriq® (mirabegron)

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